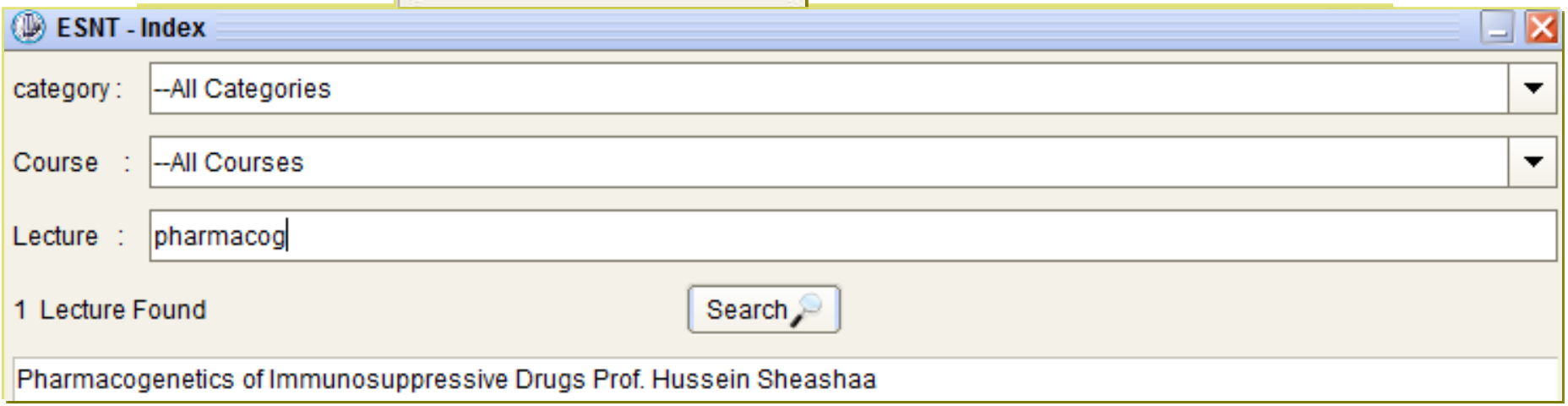
Pharmacogenetics of Immunosuppressive Drugs

Hussein Sheashaa, MD

Professor of Nephrology, Urology and Nephrology Center and Director of Medical E-Learning Unit, Mansoura University and Executive Director of ESNT- Virtual Academy: http://lms.mans.edu.eg/esnt/

January 15th, 2015

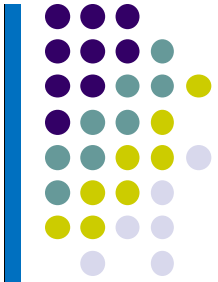


Conferences and Meetings

The ESNT 10th Organ Transplantation Jan 31- Feb 1, 2013 Update

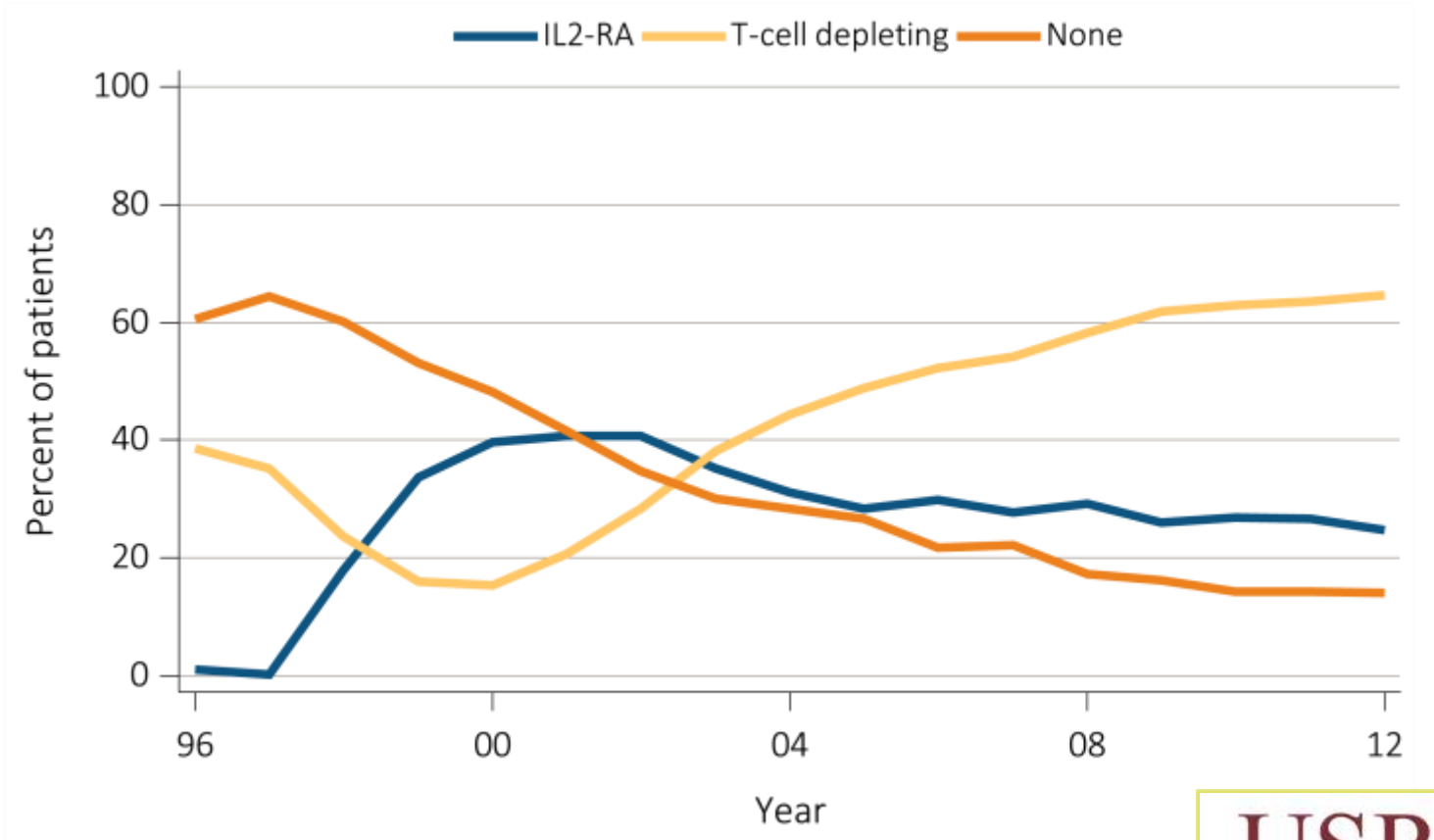
http://lms.mans.edu.eg/esnt/pluginfile.php/3176/mod_resource/content/1/Pharmacogenetics%20of%20IS%20Jan%2031%2C%20...

Focus of The Talk



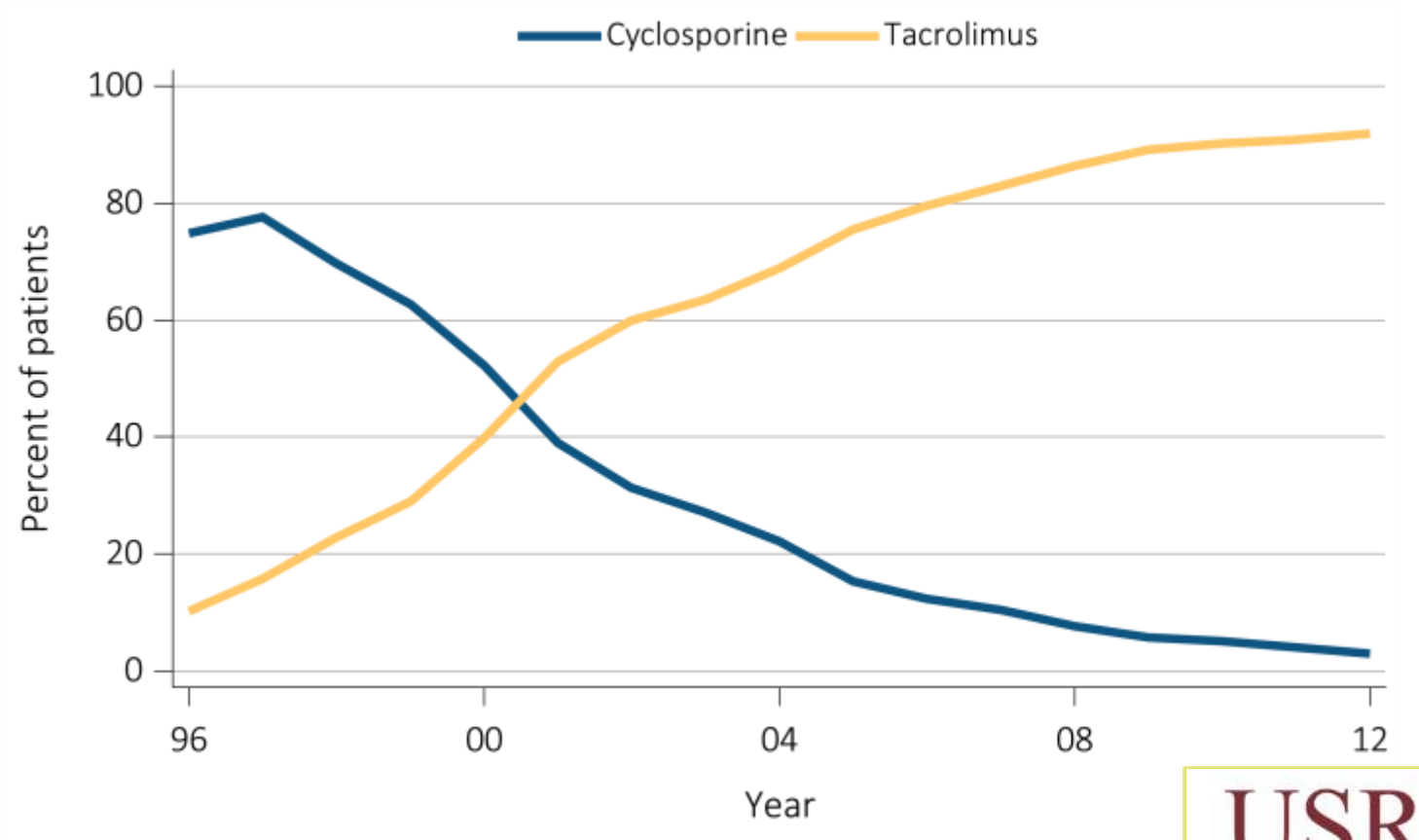
- Current immunosuppression
- Personalized medicine
- CYP polymorphism
- ABCB polymorphism
- Conclusion

Current Immunosuppression: Induction



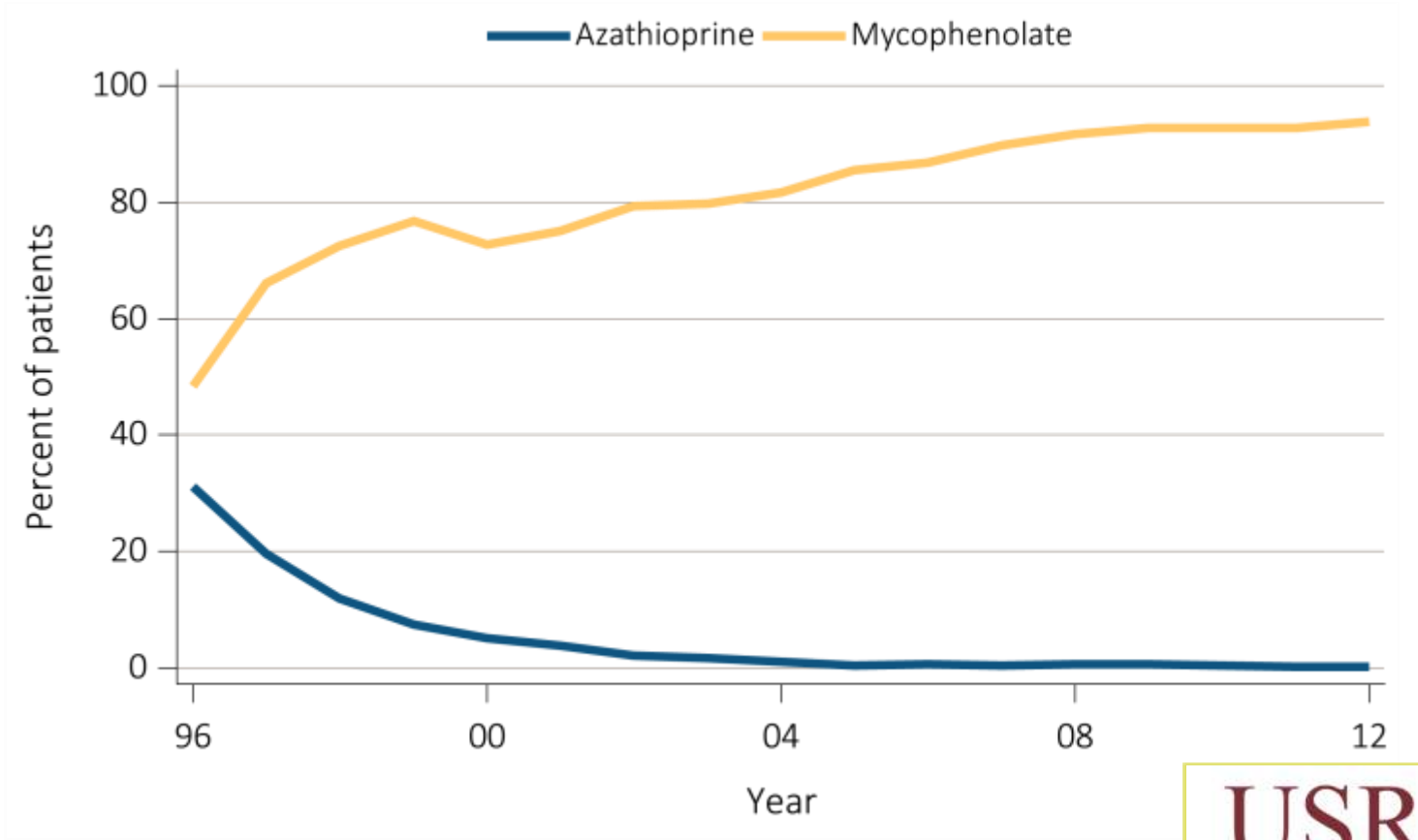
USRDS
UNITED STATES RENAL DATA SYSTEM
2014 ANNUAL DATA REPORT

Current Immunosuppression: CNI



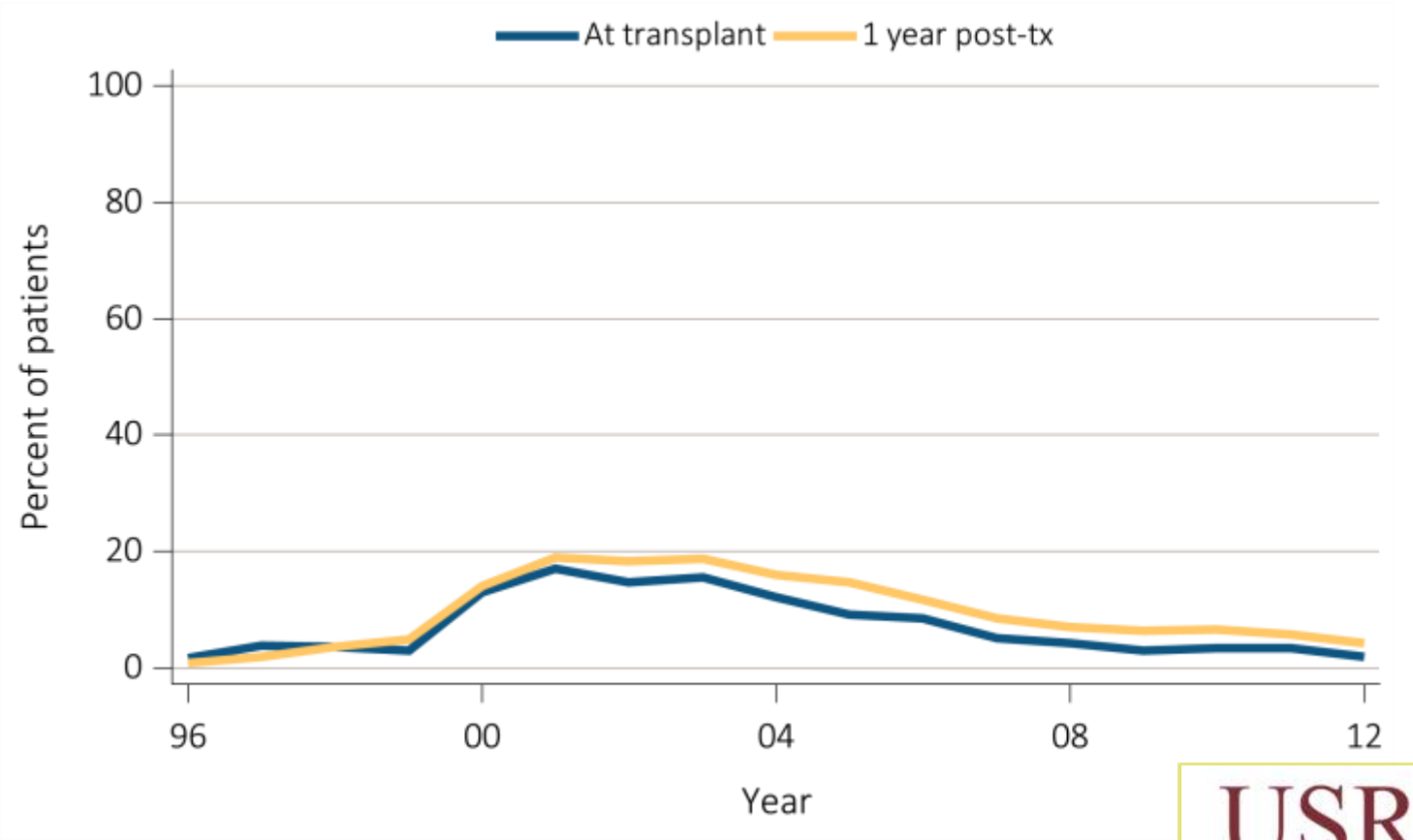
USRDS
UNITED STATES RENAL DATA SYSTEM
2014 ANNUAL DATA REPORT

Current Immunosuppression: Antiproliferative



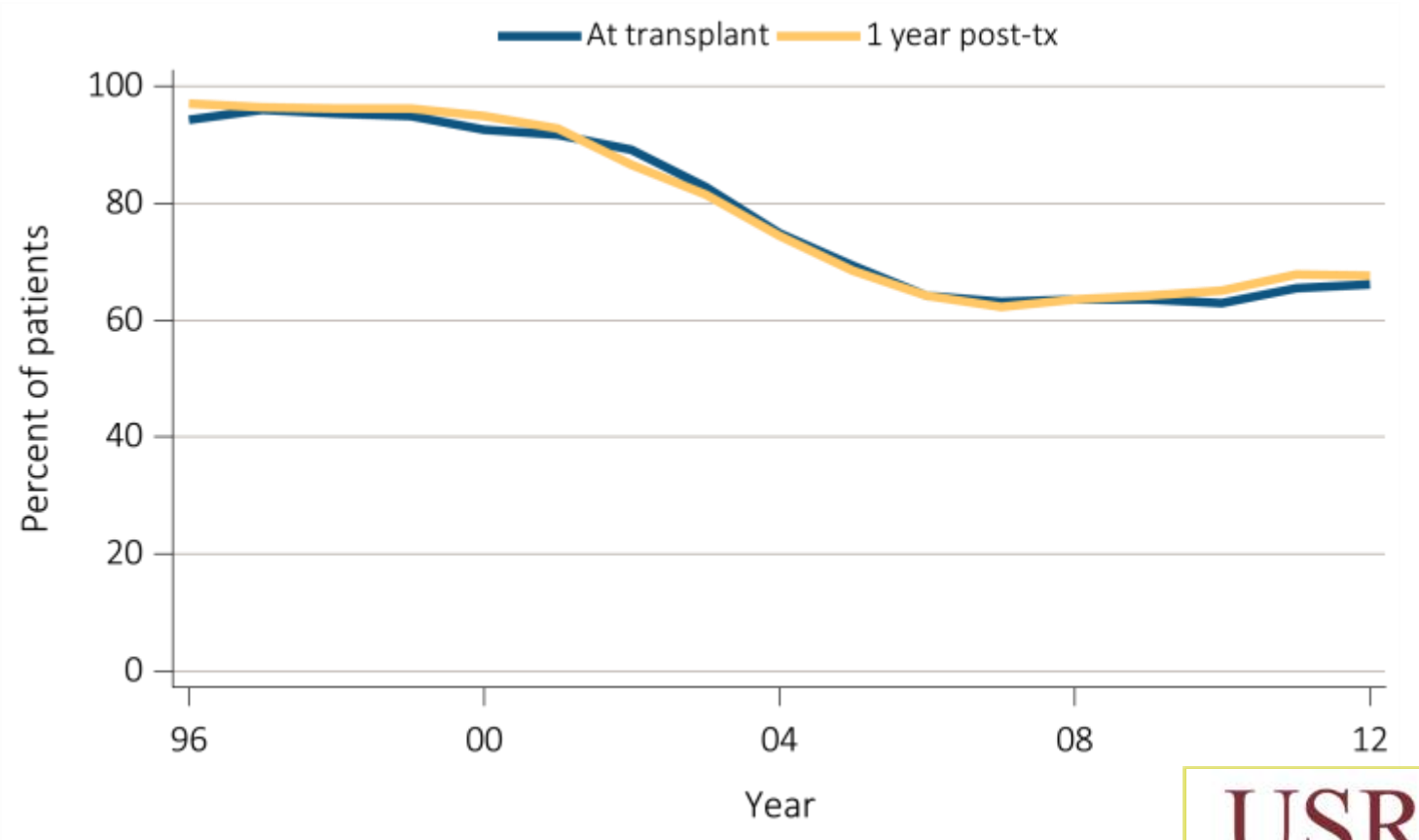
USRDS
UNITED STATES RENAL DATA SYSTEM
2014 ANNUAL DATA REPORT

Current Immunosuppression: mTORi



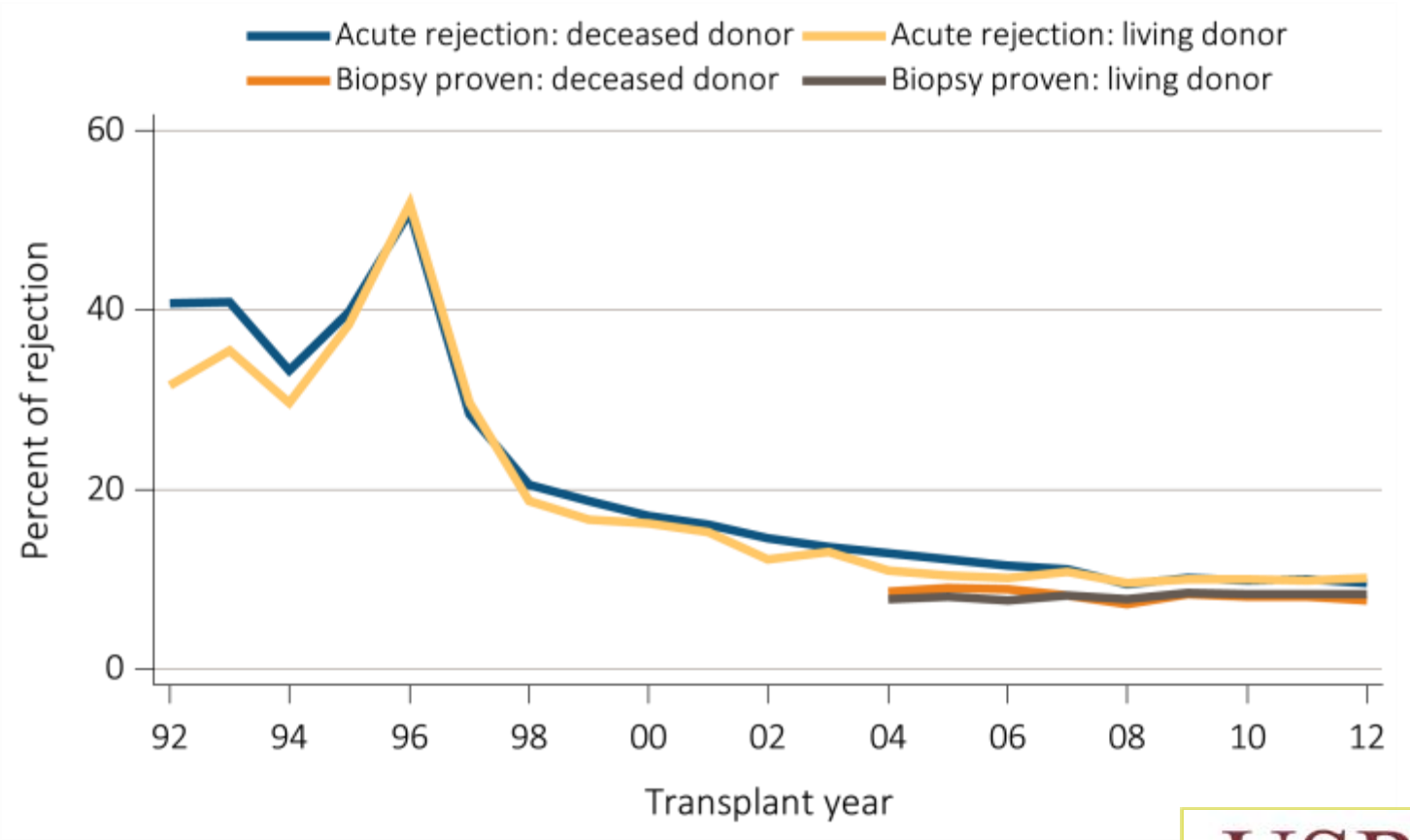
USRDS
UNITED STATES RENAL DATA SYSTEM
2014 ANNUAL DATA REPORT

Current Immunosuppression: Steroids



USRDS
UNITED STATES RENAL DATA SYSTEM
2014 ANNUAL DATA REPORT

Acute Rejection Within First Year after Renal Transplantation



USRDS
UNITED STATES RENAL DATA SYSTEM
2014 ANNUAL DATA REPORT

Tacrolimus Discharge Levels and AR

	TAC<8 ng/mL (n=119)	TAC≥8 ng/mL (n=97)	P
Age (y), mean (SD)		50.0 (12.3)	0.99
Male, %		60.8	0.58
Caucasian, %		90.7	0.84
Prior transplant, %		30.9	0.92
Deceased donor, %		58.8	
Etiology of renal failure, %			
Glomerular disease	28.6	35.1	0.01
Diabetes	12.6	22.7	
Hypertension	10.1	9.3	
PCKD	21.9	6.2	
Other	26.9	26.8	
Prior dialysis, %	47.1	58.9	0.09
Baseline peak MFI, median (IQR)	672 (270–1194)	721 (392–1174)	0.40
Baseline non-zero PRA, %	49.6	53.6	0.56
Baseline peak PRA,[a] mean (SD)	59.6 (31.8)	60.5 (34.6)	0.89
Basiliximab induction, %	58.8	53.6	0.44

2 Folds: BPAR

[a] Among those with non-zero baseline peak PRA.

DDRT, deceased donor renal transplant; IQR, interquartile range; MFI, mean fluorescence intensity; PCKD, polycystic kidney disease; PRA, panel-reactive antibody; SD, standard deviation; TAC, tacrolimus.

Transplantation 2014;97: 986-991

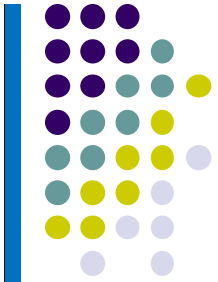
Personalized Medicine: Genetics

Direct-to-consumer genetic profiling services

	Genotyping		Genome sequencing
	Pathway Genomics	Genetics Testing Laboratories (GTL)	Illumina
URL	www.pathway.com	www.gtldna.com	www.everygenome.com
Platform/variant content	Selected SNP panel	Selected SNP panel	Whole genome, or exome SNPs, ±indels, ±CNVs
Data interpretation services	Yes	Yes	No
Genetic counseling services	Available	Available	No
Ancestry services	No	Yes	Data, no analysis
Number of traits characterized	Carrier status: 76 Complex traits: 81 Drugs: 10	Complex traits: 25	1600 genes for 1221 conditions
Direct consumer access	No (via clinician)	Yes	Yes
Cost*	Not applicable	$315 for traits	$5000 to 17,500

- **Direct-to-consumer testing**

Personalized Medicine: Omics



- Gene expression profiling (also referred to as transcriptomics)
- Proteomics
- Metabolomics
- Lipidomics

Pharmacogenomics

REVIEW ARTICLE

GENOMIC MEDICINE

W. Gregory Feero, M.D., Ph.D., and Alan E. Guttmacher, M.D., *Editors*

Genomics and Drug Response

Liewei Wang, M.D., Ph.D., Howard L. McLeod, Pharm.D.,
and Richard M. Weinshilboum, M.D.

PHARMACOGENOMICS IS THE STUDY OF THE ROLE OF INHERITED AND ACquired genetic variation in drug response.

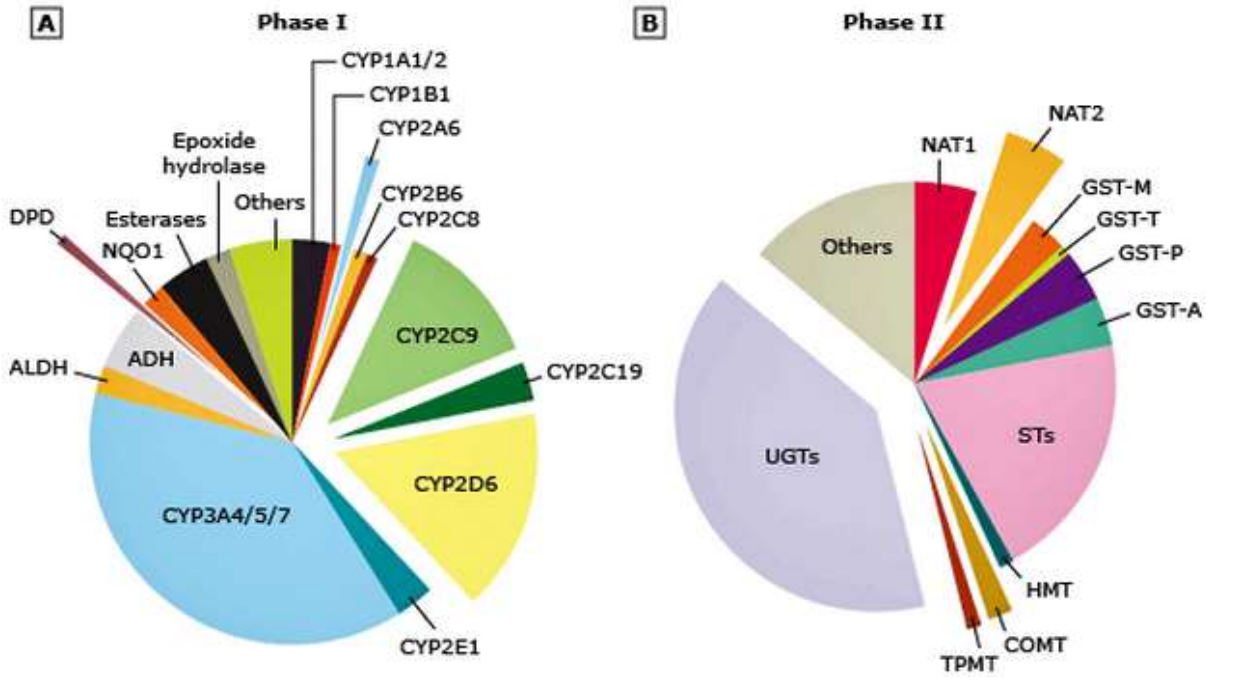
N Engl J Med 2011;364:1144-53.

Pharmacogenomic Influences on Drug Response

1. Pharmacokinetics
2. Pharmacodynamics
3. Idiosyncratic reactions
4. Pathogenesis or severity and response to specific therapies

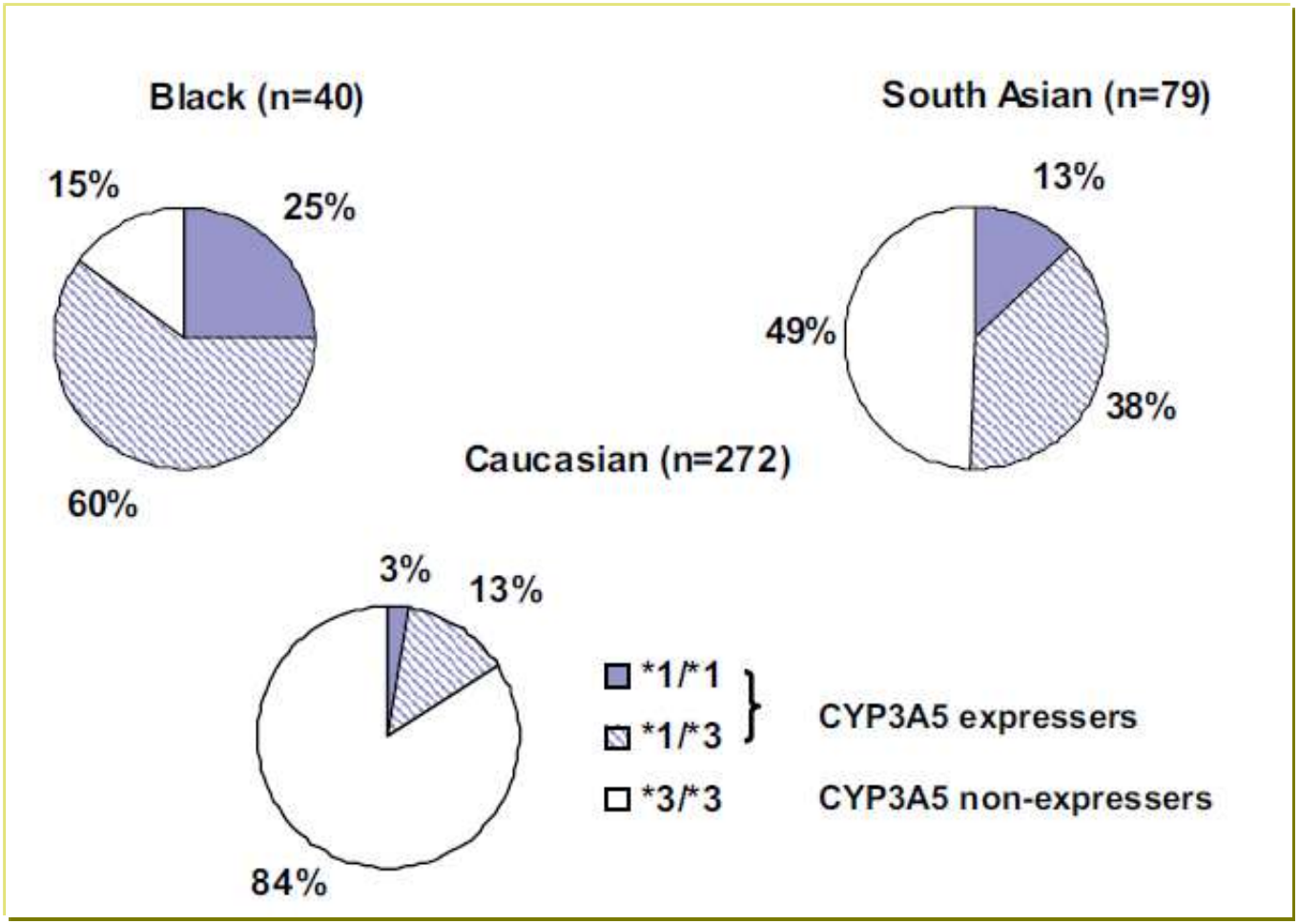
Drug Metabolism

Drug-metabolizing enzymes exhibiting clinically relevant genetic polymorphisms



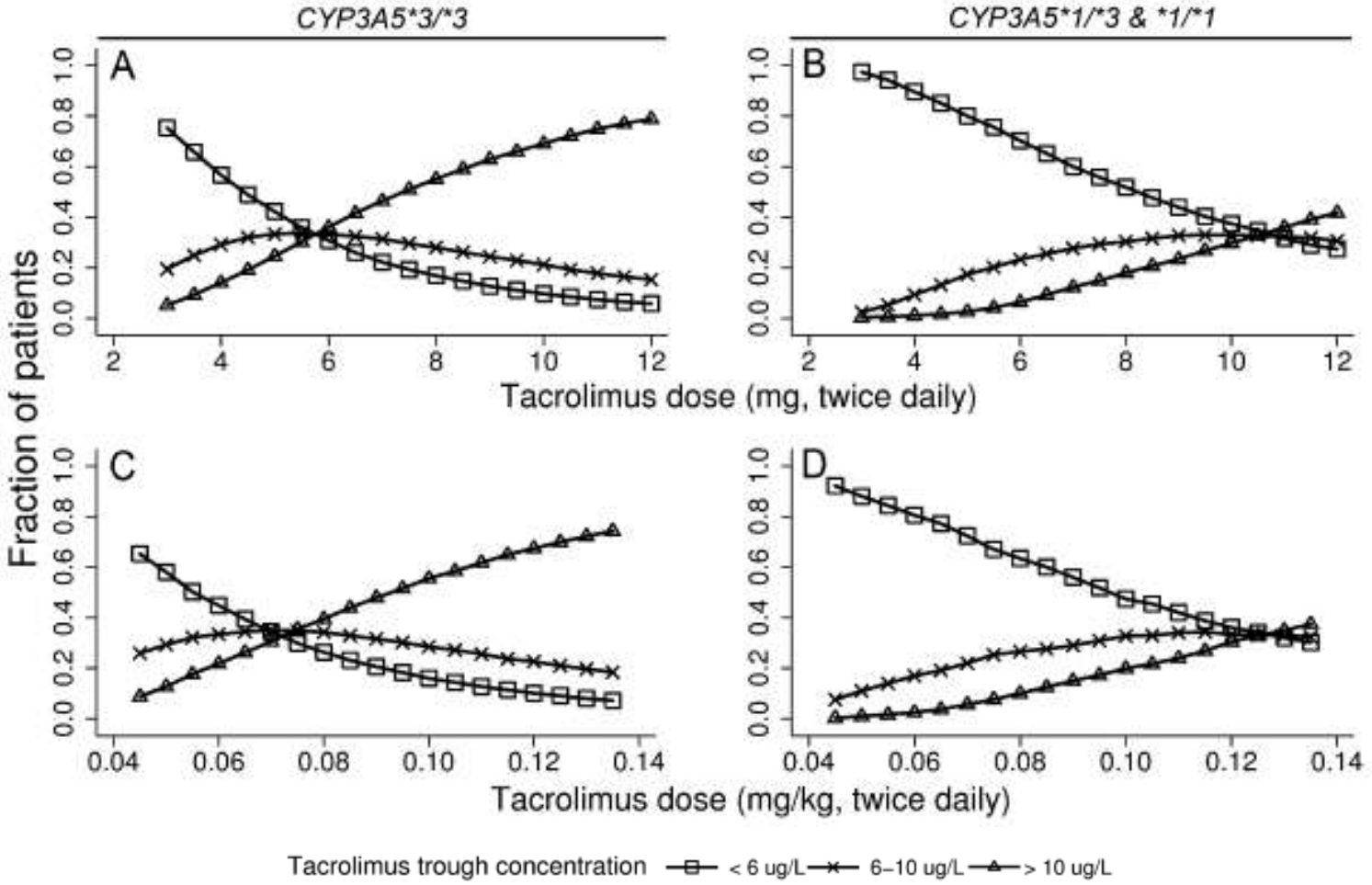
Science 1999; 286:487.

CYP3A5



Transplantation 2008;85: 163–165 . Review

CYP3A5 and Tacrolimus



Ther Drug Monit 2014;36:62–70

CYP3A5 and Tacrolimus:

In Pediatric Transplant Recipients

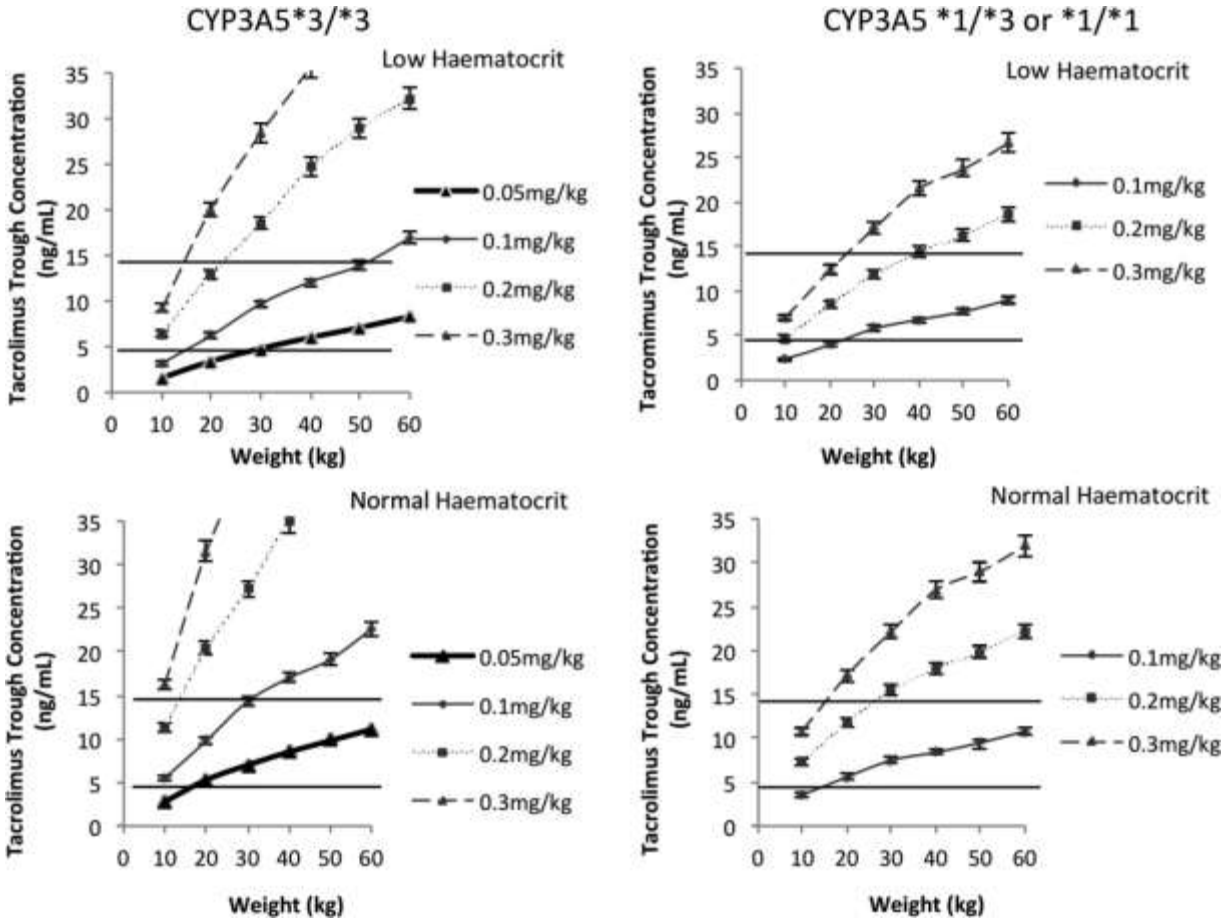
Table 5 Tacrolimus dosage for CYP3A5 expresser and non-expresser

Study	Time post-transplantation	Dosage of tacrolimus (mg/kg/day)		Ratio†
		CYP3A5*1 carriers	CYP3A5*3/*3	
Renal transplantation				
Tada *et al*[30]	1 M	0.271±0.110	0.150±0.056	1.8
Ferraresso *et al*[32]	1 W	0.26 (0.1–0.36)	0.21 (0.12–0.41)	1.2
	2 W	0.3 (0.13–0.3)	0.24 (0.05–0.36)	1.3
	1 M	0.3 (0.11–0.5)	0.18 (0.03–0.44)	1.7
	2 M	0.26 (0.1–0.38)	0.16 (0.05–0.36)	1.6
	7 M	0.19 (0.11–0.35)	0.11 (0.05–0.27)	1.7
	13 M	0.19 (0.08–0.32)	0.08 (0.03–0.22)	2.4
Turolo *et al*[35]	1 W	0.28±0.02	0.22±0.1	1.3
	1 M	0.44±0.16	0.24±0.1	1.8
	2 M	0.4±0.12	0.18±0.08	2.2
de Wildt *et al*[36]	2 W	0.28 (0.14–0.42)	0.18 (0.02–0.70)	1.6
Ferraris *et al*[37]	12 M	0.21±0.03	0.13±0.01	1.6
García-Roca *et al*[40]	6 M	0.17 for CYP3A5*1/*1 0.14 for CYP3A5 *1/*3	0.07	2.0‡
Heart transplantation				
Gijsen *et al*[38]	2 W	0.28	0.12	2.3
Liver transplantation				
Durand *et al*[41]	Steady-state	0.29±0.20	0.18±0.23	1.6

Arch Dis Child 2014;0:1–8.

CYP3A5 and Tacrolimus:

In Pediatric Transplant Recipients



Arch Dis Child 2014;0:1–8.
Clin Pharmacol Ther 2009;86:609–18.

CYP3A5 and Tacrolimus:
Liver Transplantation

TABLE 5. Difference in Tacrolimus C_0/Dose Ratio in Paired Donor and/or Recipient Expressers of CYP3A5 (Group 1) Versus Paired Donor and Recipient Nonexpressers (Group 2)

Time After Transplant	Group 1 Paired Genotype (Donor:Recipient)	Group 2 Paired Genotype (Donor:Recipient)	No. Studies Included	n	WMD	95% Confidence Interval	I_2, %
7 d*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	2	56	−1.968	−4.283 to 0.347	91
14 d*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	2	56	−1.133	−1.861 to 0.405	33
1 mo*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	2	56	−1.076	−1.659 to 0.493	0
2 mo*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	1	36	−2.124	−2.981 to 1.266	NA
3 mo*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	1	36	−2.394	−3.291 to 1.497	NA
6 mo*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	1	36	−3.688	−4.806 to 2.571	NA
12 mo*	*1/*1 or *1/*3:*3/*3	*3/*3:*3/*3	1	36	−3.266	−4.307 to 2.226	NA
Sub total					−1.933	−2.573 to 1.293	79
7 d‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	2	53	−0.866	−1.546 to 0.186	12
14 d‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	2	53	−1.840	−4.506 to 0.826	92
1 mo‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	2	53	−1.337	−3.330 to 0.656	88
2 mo‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	1	30	−2.789	−3.943 to 1.634	NA
3 mo‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	1	30	−2.247	−3.318 to 1.177	NA
6 mo‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	1	30	−4.306	−5.746 to 2.867	NA
12 mo‡	*3/*3:*1/*1 or *1/*3	*3/*3:*3/*3	1	30	−2.574	−3.694 to 1.454	NA
Sub total					−1.942	−2.724 to 1.161	83

*Donor *1/*1 or *1/*3 genotype and recipient *3/*3 genotype compared with donor *3/*3 genotype and recipient *3/*3 genotype.
†Donor *1/*1 or *1/*3 genotype and recipient *1/*1 or *1/*3 genotype compared with donor *3/*3 genotype and recipient *3/*3 genotype.
‡Donor *3/*3 genotype and recipient *1/*1 or *1/*3 genotype compared with donor *3/*3 genotype and recipient *3/*3 genotype.
I_2, percentage of total variation across studies; NA, not available; WMD, weighted mean differences in tacrolimus C0/dose values.

Ther Drug Monit 2014;36:442–447)

CYP3A5 and Tacrolimus:

In Cardiac Transplantation

	CYP3A5 Expressors	n*	CYP3A5 Nonexpressors	n*	*P*
Dose ($mg \cdot kg^{-1} \cdot d^{-1}$)					
1 mo	0.24 (0.16–0.35)	11	0.11 (0.09–0.17)	35	**0.003**
3 mo	0.22 (0.17–0.28)	8	0.09 (0.06–0.13)	32	**<0.001**
6 mo	0.21 (0.16–0.23)	6	0.08 (0.06–0.11)	34	**<0.001**
12 mo	0.16 (0.11–0.18)	6	0.07 (0.05–0.09)	29	**<0.001**
C_0 (ng/mL)					
1 mo	13.4 (10.4–15.4)	11	12.8 (11.5–15.9)	35	0.51
3 mo	10.6 (10.0–13.0)	8	12.6 (11.2–14.1)	32	0.15
6 mo	13.9 (11.8–14.9)	6	11.8 (10.2–13.5)	34	0.12
12 mo	9.5 (7.9–12.8)	6	12.6 (11.2–15.5)	29	0.07
Dose-adjusted C_0 [(ng/mL)/ ($mg \cdot kg^{-1} \cdot d^{-1}$)]					
1 mo	61.2 (43.0–71.9)	11	122.2 (85.2–154.0)	35	**0.001**
3 mo	43.1 (37.9–77.7)	8	139.1 (116.1–186.8)	32	**<0.001**
6 mo	61.1 (54.1–93.0)	6	149.3 (114.8–205.4)	34	**<0.001**
12 mo	64.8 (49.9–84.1)	6	206.3 (141.0–245.3)	29	**<0.001**

Ther Drug Monit Dec 2014;36:710–715

GENECUBE

Therapeutic Drug Monitoring Publish Ahead of Print
DOI: 10.1097/FTD.0000000000000182

Title: Effect of genetic polymorphism of *CYP3A5* and *CYP2C19*, and concomitant use of voriconazole on blood tacrolimus concentration in patients receiving hematopoietic stem cell transplantation

TABLE 3. Multivariate logistic regression analysis of the variables associated with an increase in tacrolimus C/D ratio above the respective median values† on days 14 and 21 (n = 21).

Day 14				Day 21			
Variables	Odds ratio	95% CI	P value	Variables	Odds ratio	95% CI	P value
*CYP3A5*3/*3*	32.2	1.32 – 786	< 0.05	Age (years)	0.898	0.772 – 1.04	0.162
Concomitant VRCZ	37.8	1.46 – 976	< 0.05	*CYP3A5*3/*3*	33.0	1.34 – 814	< 0.05

CI: confidence interval

VRCZ: voriconazole

†Median tacrolimus C/D values for day 14 and day 21 are 602.1 and 729.5 ng/mL per mg/kg, respectively.

Therapeutic Drug Monitoring 2015, accepted

CYP3A5 and Tacrolimus: RCT (62:58)/ Diltiazem

Individualization of tacrolimus dosage basing on cytochrome P450 3A5 polymorphism – a prospective, randomized, controlled study

Clin Transplant 2013: 27: E272–E281

CYP2E1 and Rejection:
n (63 AR, 284 no AR)

Association studies of cytochrome P450, family 2, subfamily E, polypeptide 1 (*CYP2E1*) gene polymorphisms with acute rejection in kidney transplantation recipients

OR: 2.6 (1.43-4.77)

Clin Transplant 2014: 28: 707–712

KCNQ1 and Tacrolimus:
PTDM (145/260)

KCNQ1 gene variants and risk of new-onset diabetes in tacrolimus-treated renal-transplanted patients

CC genotype: OR: 1.8 (1.14-2.93)

Clin Transplant 2011: 25: E284–E291

Tacrolimus and DDI: Omeprazole Story

CASE REPORT

Pharmacogenetic Determinant of the Drug Interaction Between Tacrolimus and Omeprazole

Wei Zhao, PharmD, PhD,† May Fakhoury, PharmD, PhD,*† Anne Maisin, MD,‡ Véronique Baudouin, MD,‡ Thomas Storme, PharmD, PhD,§ Georges Deschênes, MD, PhD,‡¶ and Evelyne Jacqz-Aigrain, MD, PhD*†¶*

Ther Drug Monit 2012;34:739–741

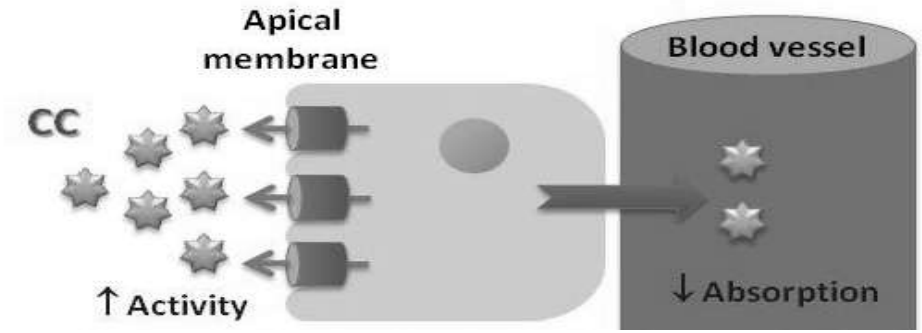
CYP3A and Tacrolimus:
n 223 (German 136; Danish 87)

Which genetic determinants should be considered for tacrolimus dose optimization in kidney transplantation? A combined analysis of genes affecting the *CYP3A* locus.

CYP3A5, CYP3A4 ***NR1I2, POR, PPARA***

Therapeutic Drug Monitoring 2015, accepted

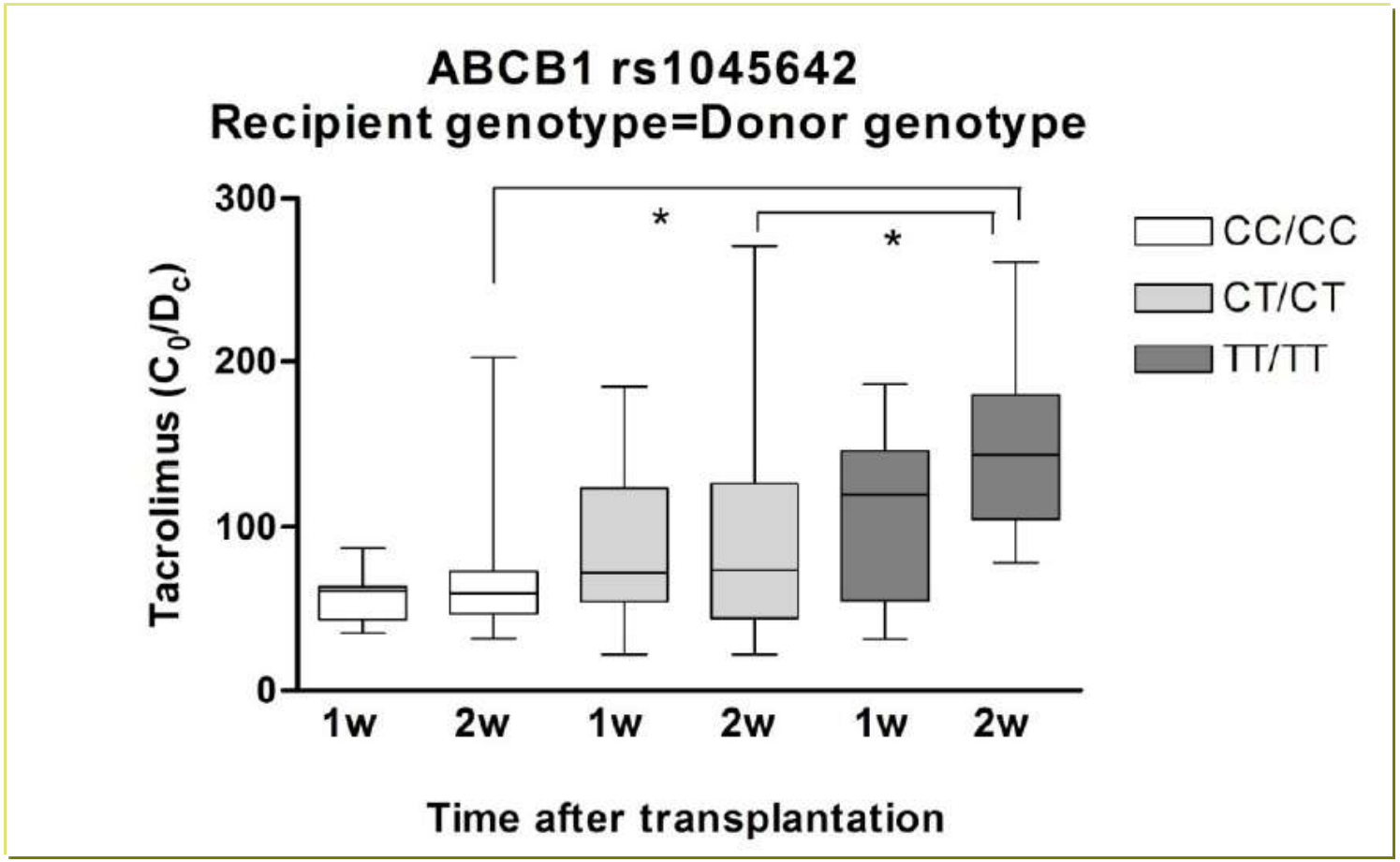
ABCB1 GP



- Functional activity of glycoprotein-P in the transport of tacrolimus in the intestine epithelium.

Renal Transplantation – Updates And Advances Textbook, 2012

ABCB1 Genetic Polymorphisms

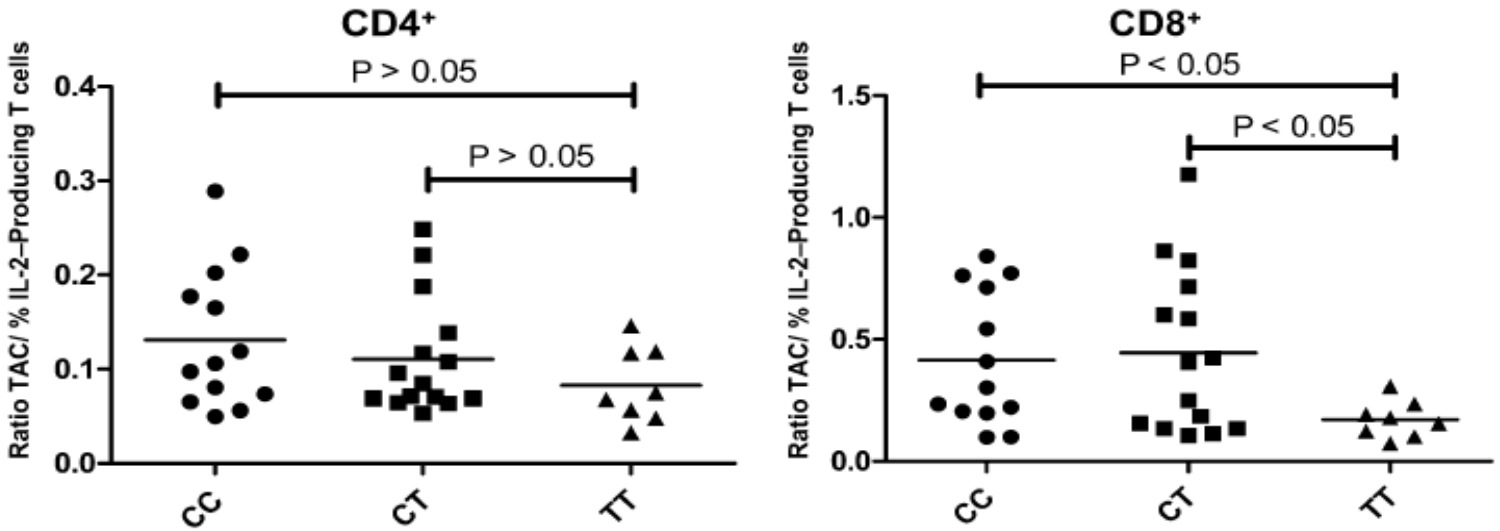


Renal Transplantation – Updates And Advances textbook, 2012

ABCB1 and Pharmacodynamics of Tacrolimus

ORIGINAL ARTICLE

Genetic Polymorphisms in ABCB1 Influence the Pharmacodynamics of Tacrolimus



Ther Drug Monit 2013;35:459–465

ABCB1 Genetic Polymorphisms

CLINICAL RESEARCH www.jasn.org

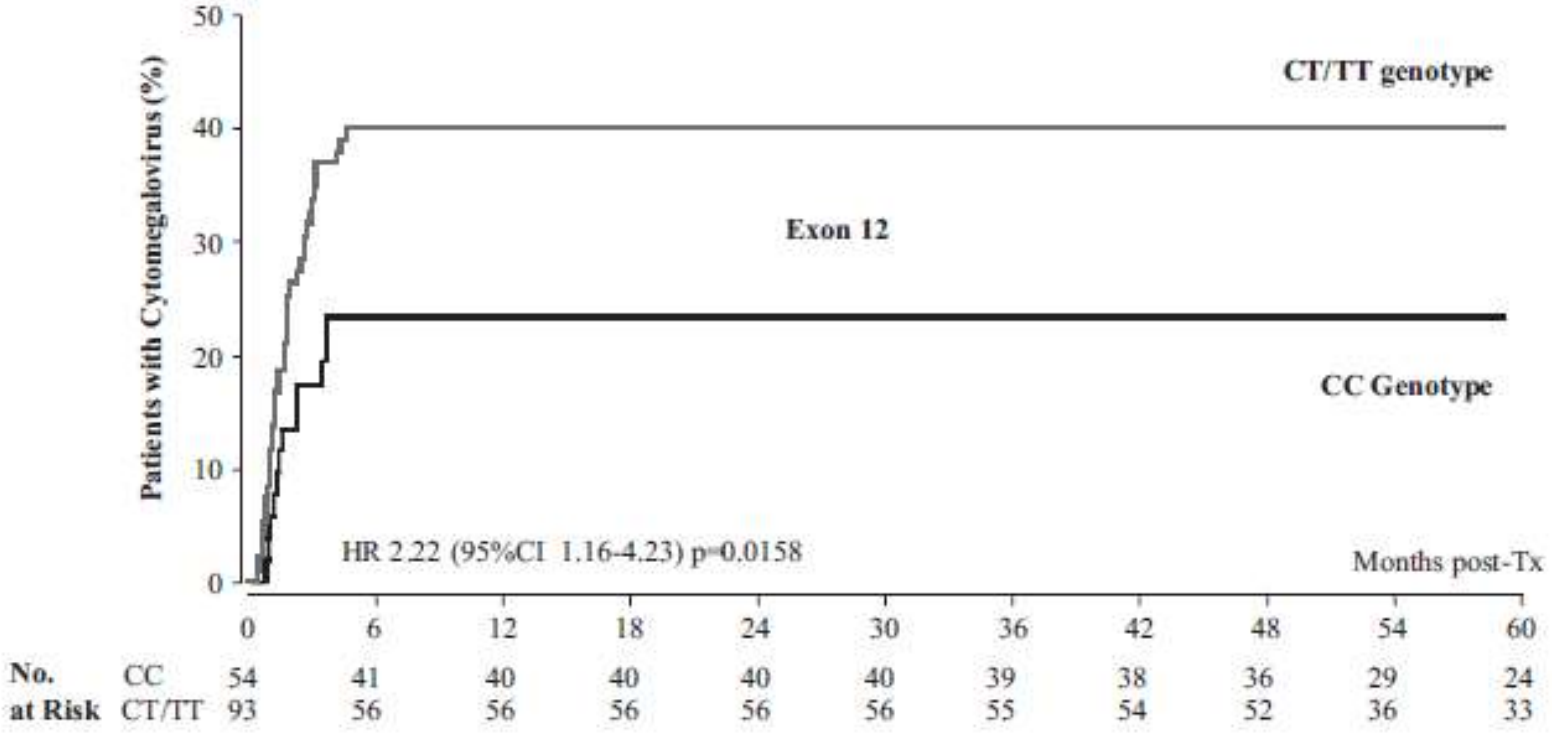
ABCB1 Genotypes Predict Cyclosporine-Related Adverse Events and Kidney Allograft Outcome

Dario Cattaneo,*† Piero Ruggenenti,*† Sara Baldelli,*† Nicola Motterlini,*‡ Eliana Gotti,* Silvio Sandrini,§ Maurizio Salvadori,‖ Giuseppe Segoloni,¶ Paolo Rigotti,** Donato Donati,†† Norberto Perico,*† and Giuseppe Remuzzi,*† for the Mycophenolate Steroids Sparing (MYSS) Genetics Study Group

*Department of Medicine and Transplantation, Ospedali Riuniti – Mario Negri Institute for Pharmacological Research, Bergamo, Italy; ‡Laboratory of Biostatistics, Mario Negri Institute for Pharmacological Research, Bergamo, Italy; †Center for Research on Organ Transplantation "Chiara Cucchi De Alessandri e Gilberto Crespi," Bergamo, Italy; §Division of Nephrology, Dialysis and Transplantation, Azienda Ospedaliera Spedali Civili, Brescia, Italy; ‖Unit of Nephrology and Dialysis, Azienda Ospedaliera Careggi Monna Tessa, Florence, Italy; ¶Unit of Nephrology, Dialysis and Transplantation, Azienda Ospedaliera S.G. Battista, Torino, Italy; **II Institute of General Surgery, Ospedale Giustinianeo, Padua, Italy; ††Unit of Nephrology and Dialysis, Azienda Ospedaliera Universitaria "Ospedale Regionale di Circolo e Fondazione Macchi," Varese, Italy

J Am Soc Nephrol 20: 1404–1415, 2009.

ABCB1 Genetic Polymorphisms



J Am Soc Nephrol 20: 1404–1415, 2009.

ABCB1 Genetic Polymorphisms

CLINICAL RESEARCH www.jasn.org

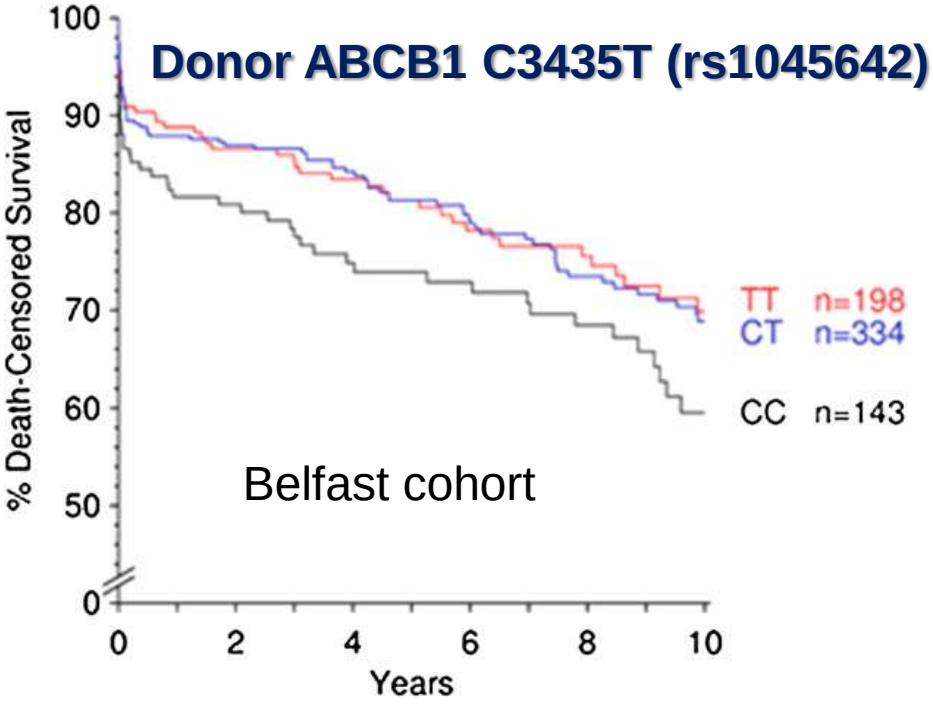
Donor *ABCB1* Variant Associates with Increased Risk for Kidney Allograft Failure

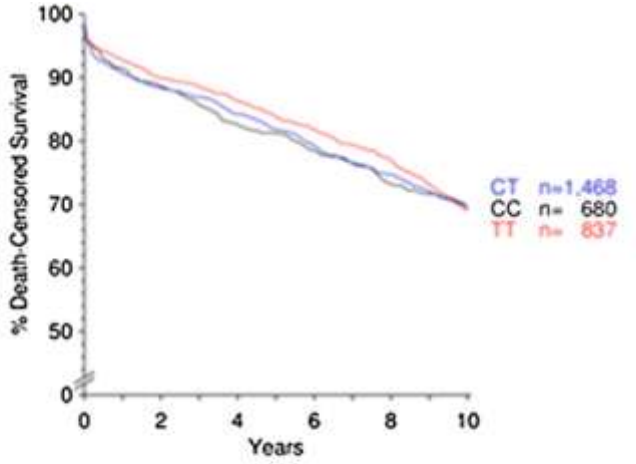
Jason Moore,*† Amy Jayne McKnight,‡ Bernd Döhler,§ Matthew J. Simmonds,‖ Aisling E. Courtney,‡ Oliver J. Brand,‖ David Briggs,¶ Simon Ball,*†† Paul Cockwell*†† Christopher C. Patterson‡ Alexander P. Maxwell,‡ Stephen C.L. Gough,‖ Gerhard Opelz,§ and Richard Borrows*††

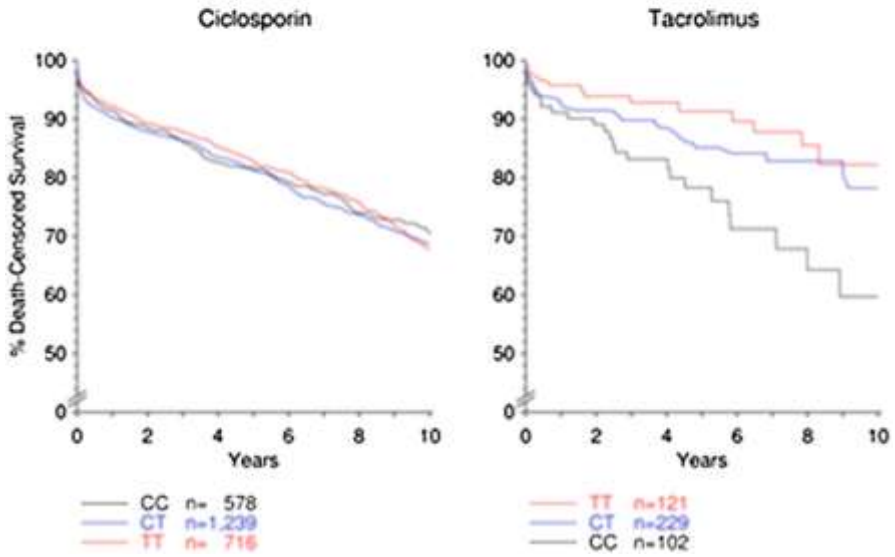
*Department of Nephrology and Transplantation, Queen Elizabeth Hospital, Birmingham, United Kingdom; †The Kidney Unit, Royal Devon and Exeter NHS Foundation Trust, Wonford Hospital, Exeter, United Kingdom; ‡Nephrology Research Group, Queen's University of Belfast, Northern Ireland, United Kingdom; §Collaborative Transplant Study Group, University of Heidelberg, Heidelberg, Germany; ‖Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Oxford, United Kingdom; ¶National Blood Service, Birmingham, United Kingdom; and ††Centre for Translational Inflammation Research, University of Birmingham, Birmingham, United Kingdom

J Am Soc Nephrol 23: 1891–1899, 2012.

ABCB1 Genetic Polymorphisms



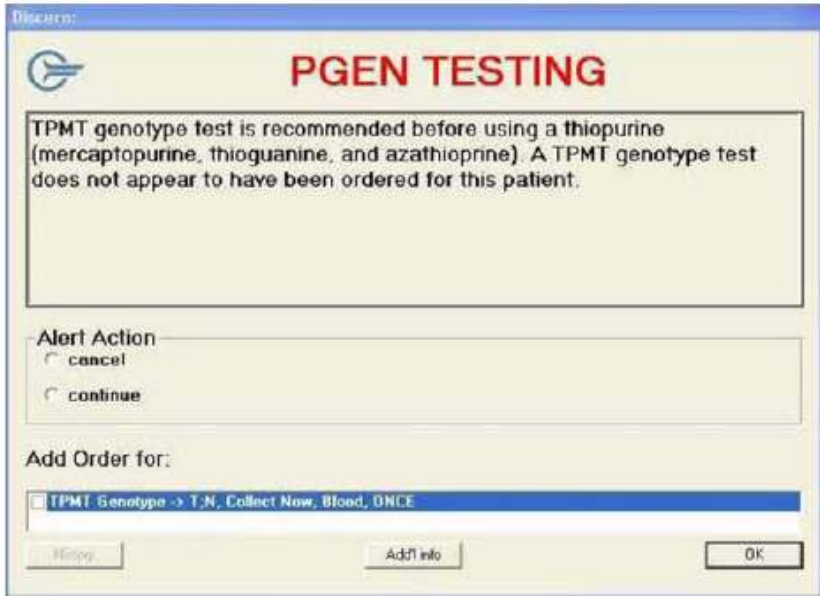


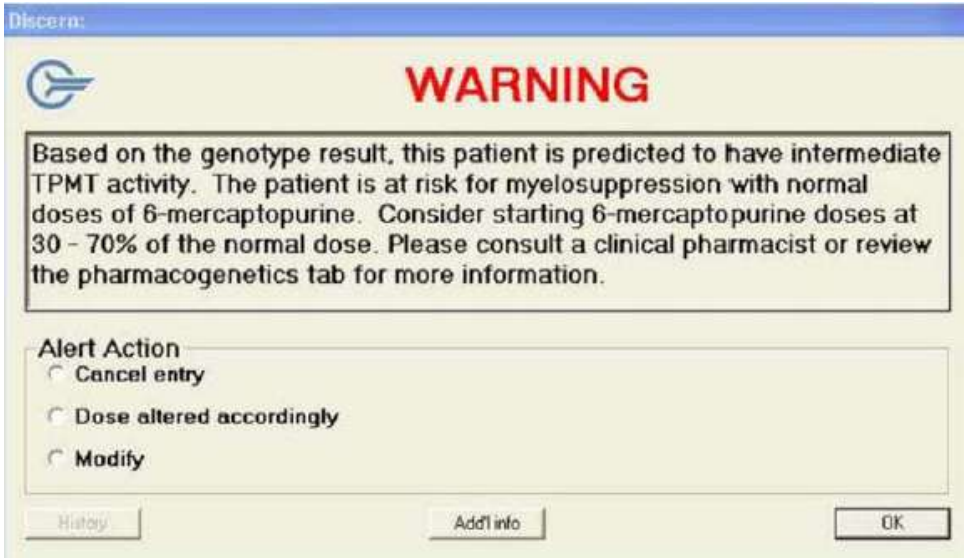


Preemptive Pharmacogenetics

Research and applications

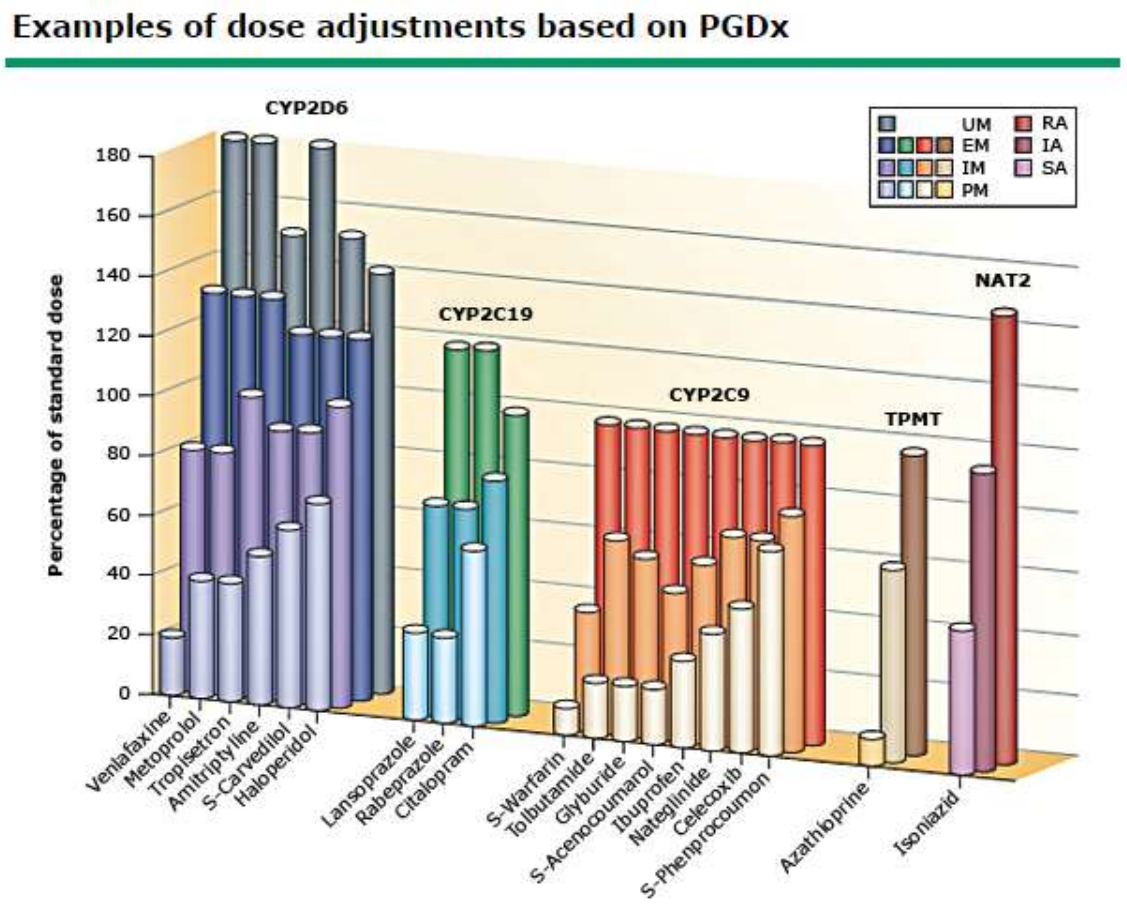
Development and use of active clinical decision support for preemptive pharmacogenomics





J Am Med Inform Assoc 2014;21:e93–e99.

TPMT



Nat Rev Drug Discov 2005; 4:639.

Pharmacogenetics: Review

Mycophenolate mofetil	*UGT1A9*	−2152C>T	rs17868320	Reduced mycophenolic acid exposure	Increased rejection risk
		−275T>A	rs6714486		
	IMPDH2	3757T>C	rs11706052	Increased IMPDH activity	No influence on rejection risk No association with graft function or survival

Nat. Rev. Nephrol. 10, 725–731 (Dec 2014);

Pharmacogenetics: Review

Drug	Gene	Polymorphism	rs number	Effect on protein activity	Clinical response
Ciclosporin	*ABCB1*	3435C>T	rs1045642	Altered ABCB1 activity	Associated with ciclosporin nephrotoxicity Associated with long-term graft survival
Tacrolimus	*CYP3A5*	*3	rs776746	Nonfunctional CYP3A5	Reduced tacrolimus dose requirement Increased risk of supratherapeutic exposure
	CYP3A4	*22	rs35599367	Reduced CYP3A4 activity	Reduced tacrolimus dose requirement Increased risk of supratherapeutic exposure
Sirolimus	*CYP3A5*	*3	rs776746	Nonfunctional CYP3A5	Reduced sirolimus dose requirement
Everolimus	*CYP3A5*	*3	rs776746	Nonfunctional CYP3A5	No clinically relevant effect on pharmacokinetics
	CYP3A4	*22	rs35599367	Reduced CYP3A4 activity	No clinically relevant effect on pharmacokinetics

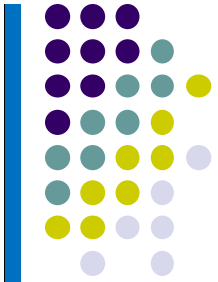
Nat. Rev. Nephrol. 10, 725–731 (Dec 2014);

CYP3A5, ABCB1 and Everolimus: In Lung Transplantation

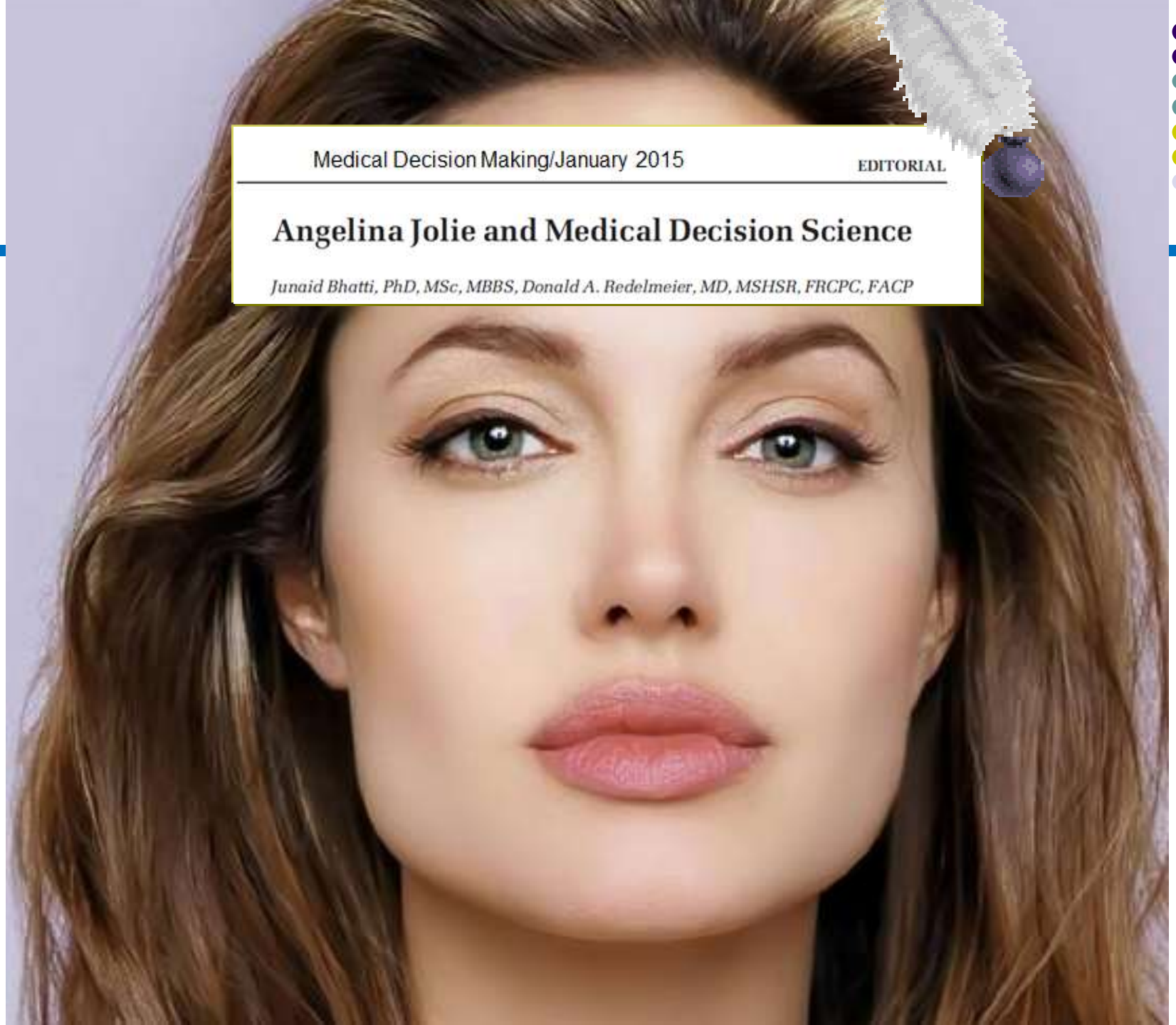
The impact of genetic polymorphisms, diltiazem, and demographic variables on everolimus trough concentrations in lung transplant recipients

Clin Transplant 2014: 28: 590–597

Pharmacogenetics:
Limitations and Challenges



- Study design
- Phenotypic/genotypic heterogeneity
- Regulatory and ethical concerns (Genetic Information Nondiscrimination Act of 2008)
- Lack of cost effectiveness analyses
- Limited availability and lack of education



Medical Decision Making/January 2015

EDITORIAL

Angelina Jolie and Medical Decision Science

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